will be pending upon entry of the present Amendment is also attached hereto as Appendix B.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

Rejection of Claims 1-9 Under 35 U.S.C. §112, First Paragraph, for Lack of Enablement

Claims 1-9 are rejected under 35 U.S.C. §112, first paragraph because, according to the Examiner, the claims are "based on a disclosure which is not enabling." In particular, the Examiner notes that "the claimed cell must be capable of coupling to (compatible with) the mammalian Gα subunit employed...[and if] one simply chooses a mammalian G protein-coupled receptor and a mammalian Gα subunit at random, the claimed yeast cell will most likely not function as disclosed."

Applicants respectfully disagree. However, without acquiescing to the rejection, Applicants have amended claim 1 (from which all the remaining rejected claims depend) to specify that the receptor and G protein of the claimed cell *are* capable of coupling, i.e., *are* compatible, by reciting in the claim that the receptor and G protein can "operatively associate." Applicants note that the ability of the heterologous receptor and heterologous G protein to operatively associate in the claimed yeast cell is discussed in detail in the specification at, for example, page 4, lines 20-34. Notably, Applicants demonstrate in working Examples 5 and 6, the ability of a heterologous receptor and heterologous G protein to operatively associate, e.g., produce an intracellular signal in a transformed yeast cell (see, e.g., pages 16-19). Accordingly, the skilled artisan, using Applicants' disclosure, would readily be able to make and use a transformed yeast cell that *would function* as claimed and disclosed.

As the Examiner is aware, it is well known that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicants respectfully submit that any experimentation that may be required to select and/or make the claimed transformed yeast cell of the invention constitutes routine, not undue, experimentation, and therefore the specification clearly enables the claims, as amended.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-9 under 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U.S.C. §103(a)

Rejection of Claims 1-7 Under 35 U.S.C. §103(a)

Claims 1-7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Marullo et al. (U.S. patent no. 5,242,822; hereafter "Marullo") in view of the Dietzel et al. (*Cell* 50:1001-1010 (1987); hereafter "Dietzel"), Herskowitz et al. (Cell 50:995-9967 (1987); hereafter "Herskowitz"), and Whiteway et al., (Cell 56:467-477 (1989); hereafter "Whiteway"). At the outset, Applicants submit that while the Examiner believes the claimed invention is not enabled, he also believes that one skilled in the art would combine various references to teach the claimed invention. Applicants submit that this "squeeze" is inappropriate.

The Examiner relies on the Marullo for teaching "the construction of an expression vector encoding a G protein-coupled receptor, a unicellular host containing that vector and a receptor ligand binding assay employing that unicellular host" and for "recommend[ing] the use of *Saccharomyces cerevisiae*." The Examiner relies on Dietzel for teaching that "it was well known in the art that a G protein α subunit was an essential component in the transduction of a signal by a G protein-coupled receptor upon the binding of a ligand by that receptor and that the α subunit specifically interacted with the cytoplasmic domains of such receptors." The Examiner relies on Herskowitz for teaching "why the yeast mating factor response system appears to be analogous [with] the G protein / G protein-coupled receptor signal transduction systems of mammals." And the Examiner relies on Whiteway for teaching "yeast homologs of mammalian Gβ and γ subunits." In combining the above *four* references, the Examiner argues it would have been obvious for the skilled artisan to have arrived at the claimed invention. Applicants respectfully disagree.

Applicants' invention is directed to a transformed yeast cell comprising a heterologous G protein coupled receptor and a heterologous G protein that can operatively associate, and for example, transduce an intracellular signal. By contrast, neither of the foregoing references either alone or in combination teach or suggest such a cell.

Regarding Marullo, the Examiner points out that "[t]he text in column 8 of this patent shows that the receptors described therein were useful only in ligand binding assays and *no mention of signal transduction is contained therein*" (emphasis added). Thus, the Examiner admits that the Marullo fails to teach or suggest the claimed invention much less provide the requisite suggestion to combine its teachings with those of the Dietzel, Herskowitz, and Whiteway.

Turning to Dietzel., the Examiner concludes "an artisan would have presumed that the rat G protein α subunit of Dietzel would transduce a signal to the recombinant yeast host cell described therein from any G protein-coupled receptor with which it could functionally interact."

Applicants respectfully disagree with the Examiner's interpretation of the results presented in Dietzel and conclusions drawn therefrom. Dietzel examined the ability of a rat $G\alpha_S$ gene to *partially* complement an *sst2* defect and *scg1* defect in yeast. Notably, however, Dietzel reports that the rat Gαs gene *cannot* properly reconstitute the pheromone response pathway and that the yeast cells are sterile, suggesting that the rat Gαs gene product is *unable* to properly interact with the yeast pheromone receptor (*i.e.*, the endogenous yeast G protein-coupled receptor). For example, Dietzel states (at page 1007, second column, second full paragraph, last sentence) that (emphasis added):

> [t]he mating defect of the *scg1* mutants expressing rat Gαs suggests that this heterologous protein is *not able to interact with activated* ***a****- or α-factor receptor;* therefore, GDP-GTP exchange would not occur in either [proposed] model [of signal transduction], *resulting in an inability to activate the pheromone response pathway, leading to sterility.*

Accordingly, Marullo and Dietzel, alone or in combination, fail to teach or suggest that a heterologous G protein coupled receptor and heterologous G protein can operatively associate to, for example, produce an intracellular signal. Marullo fails to look at intracellular events and Dietzel suggests that a G protein coupled receptor and heterologous G protein do *not* operatively associate to, for example, reliably produce an intracellular signal. The remaining references of Herskowitz and Whiteway do not make up for these deficiencies.

Indeed, Herskowitz calls in to question whether a yeast G protein coupled receptor and yeast G protein operatively associate, stating (at page 996, col. 2; emphasis added) that the:

> identification of G protein involvement is less compelling, and though appealing, cannot be considered firm. There is at present *no direct evidence for a physical or functional link between STE2 or STE3 proteins [i.e., yeast G protein coupled receptors] and the SCG1 (GPA1) gene product [i.e., a yeast G protein].*

In view of these teachings, the skilled artisan would be discouraged from looking for an operative association between a G protein coupled receptor and corresponding G protein in the same organism much less an operative association between a *heterologous*

G protein coupled receptor and a *heterologous* G protein as claimed. Thus, even in view of Whiteway, which allegedly teaches yeast homologs of mammalian Gβ and γ subunits (i.e., G proteins), the skilled artisan, in view of the above references, would not be motivated to look for an operative association between a heterologous G protein coupled receptor and heterologous G protein as claimed.

Accordingly, in view of the cited references there was no reasonable expectation, at the time the invention was made, that expression of both a heterologous G protein coupled receptor and a heterologous G protein in yeast cells would successfully reconstitute the signalling pathway, i.e., operatively associate, as now claimed.

As the Examiner is aware, a finding of obviousness relying on hindsight based on Applicants' disclosure is improper. Rather, the "critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and *the then-accepted wisdom in the field*" (emphasis added) *In re Werner Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313 (Fed. Cir. 2000). The cited references and the "then accepted wisdom in the field" do not allowed one of ordinary skill in the art to arrive at the claimed invention.

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 1-7 under 35 U.S.C. §103(a).

Rejection of Claims 8-9 Under 35 U.S.C. §103(a)

Claims 8-9 are rejected as being unpatentable over the above references as applied to claims 1-7 and further in view of Nomoto et al. (EMBO 9:691-696 (1990); hereafter Nomoto). Specifically, the Examiner states that Nomoto discloses a "yeast cell line...containing a FUS1-lacZ fusion gene" and thus, in view of the above references, it would have been obvious to the skilled artisan to have "employed a yeast cell containing a mammalian G protein-coupled receptor and a compatible mammalian Gα subunit" thereby arriving at the claimed invention (i.e., claims 8 and 9). Applicants respectfully disagree.

As claims 8-9 depend from claims 1-7, Applicants assert that the arguments made above are equally applied here. In addition, Applicants submit that Nomoto does not make up for the deficiencies noted in Marullo, Dietzel, Herskowitz, and Whiteway because Nomoto does not suggest the use of a heterologous G protein coupled receptor and heterologous G protein that can operatively associate, as now claimed. To the contrary, Nomoto is entirely directed to the use of a FUS1-lacZ fusion gene in a yeast cell having *only* yeast components of the G protein coupled receptor pathway and *not* a

heterologous G protein coupled receptor and *heterologous* G protein. Thus, for at least these reasons, claims 8-9 are inventive over the cited references.

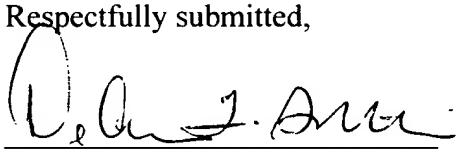
Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8-9 under 35 U.S.C. §103(a).

SUMMARY

In view of the foregoing remarks, reconsideration of the rejections and allowance of the claims is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



DeAnn F. Smith, Esq.
Reg. No. 36,683
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: June 10, 2002

OIPE JUN 17 2002 PATENT & TRADEMARK OFFICE

APPENDIX A

MARKED UP VERSION TO SHOW CHANGES MADE

1. (Amended) A transformed yeast cell containing a first heterologous DNA sequence which codes for a ~~mammalian~~ heterologous G protein coupled receptor and a second heterologous DNA sequence which codes for a ~~mammalian~~ heterologous G protein α subunit (~~mammalian~~ G_α), wherein said first and second heterologous DNA sequences are capable of expression in said cell and can operatively associate, and wherein said cell is incapable of expressing an endogenous G protein α-subunit (yeast G_α).

4. (Amended) A transformed yeast cell according to claim 1, wherein said ~~mammalian~~ heterologous G protein α subunit is selected from the group consisting of G_S α subunits, G_L α subunits, G_o α subunits, G_Z α subunits, and transducin α subunits.

7. (Amended) A transformed yeast cell according to claim 1, wherein said first heterologous DNA sequence codes for a ~~mammalian~~ heterologous G protein-coupled receptor selected from the group consisting of dopamine receptors, muscarinic cholinergic receptors, α-adrenergic receptors, β-adrenergic receptors, opiate receptors, cannabinoid receptors, and serotonin receptors.

COPY OF PAPERS
ORIGINALLY FILED

APPENDIX B

1. A transformed yeast cell containing a first heterologous DNA sequence which codes for a heterologous G protein coupled receptor and a second heterologous DNA sequence which codes for a heterologous G protein α subunit (G_α), wherein said first and second heterologous DNA sequences are capable of expression in said cell and can operatively associate, and wherein said cell is incapable of expressing an endogenous G protein α-subunit (yeast G_α).

2. A transformed yeast cell according to claim 1, wherein said first heterologous DNA sequence is carried by a plasmid.

3. A transformed yeast cell according to claim 1, wherein said second heterologous DNA sequence is carried by a plasmid.

4. A transformed yeast cell according to claim 1, wherein said heterologous G protein α subunit is selected from the group consisting of G_S α subunits, G_L α subunits, G_o α subunits, G_Z α subunits, and transducin α subunits.

5. A transformed yeast cell according to claim 1 which expresses a complex of the G protein β subunit and the G protein τ subunit ($G_{\beta\tau}$).

6. A transformed yeast cell according to claim 5 which expresses endogenous $G_{\beta\tau}$.

7. A transformed yeast cell according to claim 1, wherein said first heterologous DNA sequence codes for a heterologous G protein-coupled receptor selected from the group consisting of dopamine receptors, muscarinic cholinergic receptors, α-adrenergic receptors, β-adrenergic receptors, opiate receptors, cannabinoid receptors, and serotonin receptors.

8. A transformed yeast cell according to claim 1 further comprising a third heterologous DNA sequence, wherein said third heterologous DNA sequence comprises a pheromone-responsive promoter and an indicator gene positioned downstream from said pheromone-responsive promoter and operatively associated therewith.

9. A transformed yeast cell according to claim 8, wherein said pheromone responsive promoter is selected from the group consisting of the BAR1 gene promoter and the FUS1 gene promoter, and wherein said indicator gene is selected from the group consisting of the HIS3 gene and the LacZ gene.